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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 8

Complete if Known	
Application Number	**09/782,721**
Filing Dat	**February 12, 2001**
First Named Inv ntor	**H. Michael SHEPARD**
Art Unit	1623 ~~1653~~
Examiner Name	**L. Crane**
Attorney Docket Number	**NB 2004.02**

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number – Number – Kind Code[2] (if known)	Publication Date MM-DD-YY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US-4,247,544	01-27-81	Bergstrom, et al.	
	2	US-4,267,171	04-12-81	Bergstrom, et al.	
	3	US-4,542,210	09-17-85	Sakata et al.	
	4	US-4,816,570	03-28-89	Farquhar	
	5	US-4,948,882	08-14-90	Ruth	
	6	US-4,975,278	12-04-90	Senter et al.	
	7	US-5,085,983	02-04-92	Scanlon	
	8	US-5,233,031	08-03-92	Borch et al.	
	9	US-5,264,618	11-23-93	Felgner et al.	
	10	US-5,459,127	10-17-85	Felgner et al.	
	11	US-5,521,161	05-28-96	Malley et al.	
	12	US-5,627,165	05-06-97	Glazier	
	13	US-5,645,988	07-08-97	Vande Woude et al.	
	14	US-5,663,321	09-02-97	Gmeiner et al.	
	15	US-5,798,340	08-25-98	Bischofberger et al.	
	16	US-5,981,507	11-09-99	Josephson et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document – Country Code[3] – Number[4] – Kind Code[5] (if known)	Publication Date MM-DD-YY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
~~**~~	~~17~~	~~GB 982 776~~	02/10/65	The Wellcome Foundation		
	18	WO 91/17424	11/14/91	Vical, Inc.		
	19	WO 94/03467	02/17/94	Institute of Organic Chemistry & Biochemistry of the Academy of Sciences of the Czech Republic, Rega Stichting VZW and Gilead Sciences, Inc.		
	20	WO 96/29336	06/26/96	Amersham International, PLC		
	21	WO 96/40088	12/19/96	Hostetler, Karl		
~~**~~	~~22~~	~~WO 97/28179~~	~~08/07/97~~	Fick, James & Israel, Mark		

** Duplicate: see pto-892 for citation of record.

Sheet 2	of	Attorney Docket Number	NB 2004.02

	23	WO 99/23118	05/14/99	The Government of the United States of American represented by The Secretary of Health & Human Services		

Examiner's Signature	L. E. Crane	Date Considered	08/20/02	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 8

Complete if Known	
Application Number	09/782,721
Filing Date	February 12, 2001
First Named Inventor	H. Michael Shepard
Art Unit	1623 ~~1653~~
Examiner Name	L. Crane
Attorney Docket Number	NB 2004.02

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher city and/or country where published	T[2]
	24 !	Abraham et al., "Synthesis and biological activity of aromatic amino acid phosphoramidates of 5-fluoro-2'-deoxyuridine and 1-*J*-arabinofuranosylcytosine: Evidence of phosphoramidase activity" *J. Med. Chem. 39*:4569-4575 (1996).	
	25 !	Akdas et al., "Glutathione S-transferase and multidrug-resistant phenotype in transitional cell carcinoma of the bladder" *Eur. Urol. 29*(4):483-486 (1996).	
	26 !	Almasan et al., "Genetic instability as a consequence of inappropriate entry into and progression through S-phase" *Can. Metastasis Rev. 14*:59-73 (1995).	
	27 !	Andersen et al., "Detection of c-erbb-2 related protein in sera from breast cancer patients" *Acta Oncol. 34*(4):499-504 (1995).	
	28 !	Anglada et al., "*N,N'*-cyclization of carbodiimides with 2-(bromomethyl)acrylic acid. A direct entry to the system 5-methylene-6*H*-pyrimidine-2,4-dione, A new class of thymine analogues" *J. Heterocycl. Chem. 33*:1259-1270 (1996).	
	29 !	Antelman et al., "Inhibition of tumor cell proliferation *in vitro* and *in vivo* by exogenous p110RB, the retinoblastoma tumor suppressor protein" *Oncogene 10*:697-704 (1995).	
	30 !	Asakura et al., "Cerium(IV) catalyzed iodination at C5 of uracil nucleosides" *Tetrahedron Lett. 29*(23):2855-2858 (1988).	
	31 !	Asakura et al., "Cerium(IV)-mediated halogenation at C-5 of uracil derivatives" *J. Org. Chem. 55*:4928-4933 (1990).	
	32 !	Ayisi et al. "Comparison of the antiviral effects of 5-methoxymethyldeoxyuridine-5'-monophosphate with adenine arabinoside-5'-monophosphate" *Antivirals Res.* 3:161-174 (1983)	
	33 !	Balzarini et al., "Incorporation of 5-substituted pyrimidine nucleoside analogues into DNA of a thymidylate synthetase-deficient murine FM3A carcinoma cell line" *Meth. Find. Exp. Clin. Pharmacol. 7*(1):19-28 (1985).	
	34 !	Balzarini, J. et al., "Thymidylate synthase is the principal target enzyme for the cytostatic activity of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine against murine mammary carcinoma (FM3A) cells transformed with the herpes simplex virus type 1 or type 2 thymidine kinase gene" *Mol. Pharmacol. 32*:410-416 (1987).	
	35 !	Balzarini et al., "Differential mechanism of cytostatic effect of (*E*)-5-(2-bromovinyl)-2'-deoxyuridine , 9-(1,3-dihydroxy-2-propoxymethyl)guanine, and other antiherpetic drugs on tumor cells transfected by the thymidine kinase gene of herpes simplex virus type 1 or type 2" *J. Biol. Chem. 268*(9):6332-6337 (1993).	
	36 !	Balzarini et al., "Anti-HIV and anti-HBV activity and resistance profile of 2',3'-dideoxy-3'-thiacytidine (3TC) and its arylphosphoramidate derivative CF 1109" *Biochem. Biophys. Res. Commun. 225*:363-369 (1996).	
	37 !	Balzarini et al., "Conversion of 2',3'-dideoxyadenosine (ddA) and 2',3'-didehydro-2',3'-dideoxyadenosine (d4A) to their corresponding aryloxyphosphoramidate derivatives markedly potentiates their activity against human immunodeficiency virus and hepatitis B virus" *FEBS Lett. 410*:324-328 (1997).	
	38 !	Banerjee et al., "Molecular mechanisms of resistance to antifolates, a review" *Acta Biochem. Pol. 42*(4):457-464 (1995).	
	39 !	Banerjee et al., "Role of E2F-1 in chemosensitivity" *Can. Res. 58*:4292-4296 (1998).	
	40 !	Barbour et al., "A naturally occurring tyrosine to histidine replacement at residue 33 of human thymidylate synthase confers resistance to 5-fluoro-2'-deoxyuridine in mammalian and bacterial cells" *Mol. Pharmacol. 42*:242-248 (1992).	
	41 !	Barr, "Inhibition of thymidylate synthetase by 5-alkynyl-2'-deoxyuridylates" *J. Med. Chem. 24*(12):1385-1388 (1981).	
	42 !	Barr et al., "Thymidylate synthetase-catalyzed conversions of *E*-5-(2-bromovinyl)-2'-deoxyuridylate" *J. Biol. Chem. 258*(22):13627-13631 (1983).	
	43 !	Barr et al., "Reaction of 5-ethynyl-2'-deoxyuridylate with thiols and thymidylate synthetase" *Biochem. 22*:1696-1703 (1983).	
	44 !	Barrett, "Trapping of the C5 methylene intermediate in thymidylate synthase" *J. Am. Chem. Soc. 120*:449-450 (1998).	
	45 !	Benzaria et al., "Synthesis, *in vitro* antiviral evaluation, and stability studies of bis(*S*-acyl-2-thioethyl) ester derivatives of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) as potential PMEA prodrugs with improved oral bioavailability" *J. Med. Chem. 39*:4958-4965 (1996).	
	46 !	Bergstrom et al., "C-5-substituted pyrimidine nucleosides. 3. Reaction of allylic chlorides, alcohols, and acetates with pyrimidine nucleoside derived organopalladium intermediates" *J. Org. Chem. 46*(7):1432-1441 (1981).	
	47 !	Bergstrom et al., "Synthesis of (*E*)-5-(3,3,3-trifluoro-1-propenyl)-2'-deoxyuridine and related analogues: Potent and unusually selective antiviral activity of (*E*)-5-(3,3,3-trifluoro-1-propenyl)-2'-deoxyuridine against herpes simplex virus type 1" *J. Med. Chem. 27*:279-284 (1984).	
	48 !	Bertino et al., "Resistance mechanisms to methotrexate in tumors" *Stem Cells 14*:5-9 (1996).	

! Month of publication data is unavailable for this citation.

OTHER PRIOR ART – NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher city and/or country where published	T[2]
	49 !	Bigge et al., "Palladium-catalyzed coupling reactions of uracil nucleosides and nucleotides" *J. Amer. Chem. Soc. 102*:2033-2038 (1980).	
	50 !	Bosslet t al., "A novel one-step tumor-selective prodrug activation system" *Tumor Targeting 1*:45-50 (1995).	
	51 !	Bosslet et al., "Elucidation of the mechanism enabling tumor selective prodrug monotherapy" *Can. Res. 58*:1195-1201 (1998).	
	52 !	Brison, "Gene amplification and tumor progression" *Biochem. Biophys. Acta 1155*:25-41 (1993).	
	53 !	Carl et al., "Protease-activated 'prodrugs' for cancer chemotherapy" *PNAS USA 77*(4):2224-2228 (1980).	
	54 !	Carreras et al., "The catalytic mechanism and structure of thymidylate synthase" *Ann. Rev. Biochem. 64*:721-762 (1995).	
	55 !	Carter et al., "Humanization of an anti-p185HER2 antibody for human cancer therapy" *PNAS USA 89*:4285-4289 (1992).	
	56 !	Cava et al., "Thionation reactions of lawesson's reagents" *Tetrahedron 41*(22):5061-5087 (1985).	
	57 !	Chakravarty et al., "Plasmin-activated prodrugs for cancer chemotherapy. 2. Synthesis and biological activity of peptidyl derivatives of doxorubicin" *J. Med. Chem. 26*(5):638-644 (1983).	
	58 !	Chaudhuri et al., "Very high affinity DNA recognition by bicyclic and cross-linked oligonucleotides" *J. Am. Chem. Soc. 117*:10434-10442 (1995).	
	59 !	Chen et al., "Sensitization of human breast cancer cells to cyclophosphamide and ifosfamide by transfer of a liver cytochrome P450 gene" *Can. Res. 56*:1331-1340 (1996).	
	60 !	Cho et al., "(*E*)-5-(3-oxopropen-1-yl)-2'-deoxyuridine and (*E*)-5-(3-oxopropen-1-yl)-2',3'-dideoxyuridine; New antiviral agents: Synthesis and biological activity" *Tetrahedron Lett. 35*(8):1149-1152 (1994).	
	61 !	Clarke, "Animal models of breast cancer: Their diversity and role in biomedical research" *Breast Can. Res. Treat. 39*:1-6 (1996).	
	62 !	Colacino, "Mechanisms for the anti-hepatitis B virus activity and mitochondrial toxicity of fialuridine (FIAU)" *Antiviral Res. 29*:125-139 (1996).	
	63	Collins, J.M. et al. "Suicide prodrugs activated by Thymidylate synthase: Rationale for treatment and noninvasive imaging of tumors with deoxyuridine analogues" *Clin. Cancer Res.* 5:1976-1981 (August 1999)	
	64 !	Connors, "Prodrugs in cancer chemotherapy" *Xenobiotica 16*(10/11):975-988 (1986).	
	65 !	Connors, et al., "Prodrugs in cancer chemotherapy" *Stem Cells 13*:501-511 (1995).	
	66 !	Connors, "Is there a future for cancer chemotherapy?" *Annals Oncol. 7*:445-452 (1996).	
	67 !	Copur et al., "Thymidylate synthase gene amplification in human colon cancer cell lines resistant to 5-fluorouracil" *Biochem. Pharmacol. 49*(10):1419-1426 (1995).	
	68 !	Crisp, "Synthesis of 5-alkenyl-2'-deoxyuridines via organostannanes" *Synth. Commun. 19*(11 & 12):2117-2123 (1989).	
	69 !	Dale et al., "The synthesis and enzymatic polymerization of nucleotides containing mercury: Potential tools for nucleic acid sequencing and structural analysis" *PNAS USA 70*(8):2238-2242 (1973).	
	70 !	Davisson et al., "Expression of human thymidylate synthase in *Escherichia coli*" *J. Biol. Chem. 264*(16):9145-9148 (1989).	
	71 !	Davisson et al. "Expression of human thymidylate synthase in *Escherichia coli*. (Additions and corrections)" *J. Biol. Chem. 269*(48):30740 (1994).	
	72 !	De Clercq et al., "Nucleic acid related compounds. 40. Synthesis and biological activities of 5-alkynluracil nucleosides" *J. Med. Chem. 26*:661-666 (1983).	
	73 !	Dicker et al., "Methotrexate resistance in an *in vivo* mouse tumor due to a non-active-site dihydrofolate reductase mutation" *PNAS USA 90*:11797-11801 (1993).	
	74 !	Dirven et al., "The role of human glutathione *S*-transferase isoenzymes in the formation of glutathione conjugates of the alkylating cytostatic drug thiotepa" *Can. Res. 55*:1701-1706 (1995).	
	75 !	Dorr et al., "PALA" *In*: Cancer Chemotherapy Handbook: Appleton & Lange, Norwalk, Connecticut:768-773 (1994).	
	76 !	Dunn et al., "Solution of the conformation and alignment tensors for the binding of trimethoprim and its analogs to dihydrofolate reductase: 3D-quantitative structure-activity relationship study using molecular shape analysis, 3-way partial least-squares regression, and 3-way factor analysis" *J. Med. Chem. 39*:4825-4832 (1996).	
	77 !	Dyer et al., "Nucleic Acids Chemistry: Improved and new synthetic procedures, methods, and techniques" Townsend, L. B. & Tipson, R. S., eds. (Wiley-Interscience, New York, NY) Vol. 4:79-83 (1991).	
	78 !	Eccles et al., "Significance of the c-*erbB* family of receptor tyrosine kinases in metastatic cancer and their potential as targets for immunotherapy" *Invasion Metastasis 14*(1-6):337-348 (1994-95).	
	79 !	Eisenbrand et al., "An approach towards more selective anticancer agents" *J. Synthetic Organic Chem. 10*:1246-1258 (1996).	
	80 !	Evard, A. et al. "An in vitro nucleoside analog screening method for cancer gene therapy" *Chem. Abstracts 126*:Abstract No. 26514 (1996)	
	81 !	Farquhar et al., "Synthesis and antitumor evaluation of bis[(pivaloyloxy)methyl] 2'-deoxy-5-fluorouridine 5'-monophosphate (FdUMP): A strategy to introduce nucleotides into cells" *J. Med. Chem. 37*:3902-3909 (1994).	
	82 !	Farquhar et al., "5'-[4-pivaloyloxy)-1,3,2-dioxaphosphorinan-2-yl]-2'-deoxy-5-fluorouridine: A membrane-permeating prodrug of 5-fluoro-2'-deoxyuridylic acid (FdUMP)" *J. Med. Chem. 38*:488-495 (1994).	
	83 !	Felip et al., "Overexpression of c-*erbB*-2 in epithelial ovarian cancer" *Cancer 75*(8):2147-2152 (1995).	
	84 !	Finch et al., "Radiation Injury" *In*: Harrison's Principles of Internal Medicine, 12th edition: McGraw-Hill, Inc., New York, NY:2204-2208 (1991).	

! Month of publication data is unavailabe for this citation.

OTHER PRIOR ART – NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher city and/or country where published	T[2]
JKL	85 !	Finer-Moore et al., "Refined structures of substrate-bound and phosphate-bound thymidylate synthase from *Lactobacillus casei*" *J. Mol. Biol. 232*:1101-1116 (1993).	
JKL	86 !	Finer-Moore et al., "Crystal structure of thymidylate synthase from T4 phage: Component of a deoxynucleoside triphophate-synthesizing complex" *Biochem. 33*:15459-15468 (1994).	
JKL	87 !	Firestone et al., "A comparison of the effects of antitumor agents upon normal human epidermal kerarinocytes and human squamous cell carcinoma" *Chem Abstracts 113*:Abstract No. 254 (1990)	
JKL	88 !	Freed et al., "Evidence for acyloxymethyl esters of pyrimidine 5'-deoxyribonucleotides as extracellular sources of active 5'-deoxyribonucleotides in cultured cells" *Biochem. Pharmacol. 38*(19):3193-3198 (1989).	
JKL	89 !	Fries et al., "Synthesis and biological evaluation of 5-fluoro-2'-deoxyuridine phosphoramidate analogs" *J. Med. Chem. 38*(14):2672-2680 (1995).	
JKL	90 !	Garrett et al., "Thymidylate synthetase. Catalysis of dehalogenation of 5-bromo-and 5-iodo-2'-deoxyuridylate" *Biochem. 18*(13):2798-2804 (1979).	
JKL	91 !	Goldberg et al. "Novel cell imaging techniques show induction of apoptosis and proliferation in mesothelial cells by asbestos" *Am. J. Respir. Cell Mol. Biol.* 17:265-271 (1997)	
JKL	92 !	Goldstein et al., "Genetic aspects of disease" *In*: Harrison's Principles of Internal Medicine, 12th edition: McGraw-Hill, Inc., New York, NY:21-76 (1991).	
JKL	93 !	Goodwin et al., "Incorporation of alkylthiol chains at C-5 of deoxyuridine" *Tetrahedron Lett. 34*(35):5549-5552 (1993).	
JKL	94 !	Gottesmanm et al., "Genetic analysis of the multidrug transporter" *Ann. Rev. Gen. 29*:607-649 (1995).	
JKL	95 !	Graham et al., "DNA duplexes stabilized by modified monomer residues: Synthesis and stability" *J. Chem. Soc. Perkin Trans. 1*:1131-1138 (1998).	
JKL	96 !	Gros et al., "Isolation and expression of a complementary DNA that confers mutidrug resistance" *Nature 323*:728-731 (1986).	
JKL	97 !	Gros et al., "Mammalian mutidrug resistance gene: Complete cDNA sequence indicates strong homology to bacterial transport proteins" *Cell 47*:371-380 (1986).	
JKL	98 !	Gros et al., "Isolation and characterization of DNA sequences amplified in multidrug-resistant hamster cells" *PNAS USA 83*:337-341 (1986).	
JKL	99 !	Gudkov et al., "Cloning and characterization of DNA sequences amplified in multidrug-resistant djungarian hamster and mouse cells" *Somat. Cell Mol. Genet. 13*(6):609-619 (1987).	
JKL	100 !	Hardy et al., "Atomic structure of thymidylate synthase: Target for rational drug design" *Science 235*:448-455 (1987).	
JKL	101 !	Harris et al., "Adenovirus-mediated p53 gene transfer inhibits growth of human tumor cells expressing mutant p53 protein" *Can. Gene Ther. 3*(2):121-130 (1996).	
JKL	102 !	Hashimoto et al., "Simple separation of tritiated water and [3H] deoxyuridine from [5-3H] deoxyuridine 5'-monophosphate in the thymidylate synthase assay" *Anal. Biochem. 167*:340-346 (1987).	
JKL	103 !	Hengstschläger et al., "The role of p16 in the E2F-dependent thymidine kinase regulation" *Oncogene 12*:1635-1643 (1996).	
JKL	104 !	Hobbs, "Palladium-catalyzed synthesis of alkynylamino nucleosides. A universal linker for nucleic acids" *J. Org. Chem. 54*:3420-3422 (1989).	
JKL	105 !	Horikoshi et al., "Quantitation of thymidylate synthase, dihydrofloate reductase, and DT-diaphorase gene expression in human tumors using the polymerase chain reaction" *Can. Res. 52*:108-116 (1992).	
JKL	106 !	Horn et al., "Fialuridine is phosphorylated and inhibits DNA synthesis in isolated rat hepatic mitochondria" *Antiviral Res. 34*:71-74 (1997).	
JKL	107 !	Hostetler et al., "Enhanced oral absorption and antiviral activity of 1-o-octadecyl-*sn*-glycero-3-phospho-acyclovir and related compounds in hepatitis B virus infection, *in vitro*" *Biochem. Pharmacol. 53*:1815-1822 (1997).	
JKL	108 !	Houze, "Detection of thymidylate synthase gene expression levels in formalin-fixed paraffin embedded tissue by semiquantitative, nonradioactive reverse transcriptase polymerase chain reaction" *Tumor Biol. 18*:53-68 (1997).	
JKL	109 !	Hsaio et al., "Synthesis of 5'-thymidinyl bis(1-aziridinyl)phosphinates as antineoplastic agents" *J. Med. Chem. 24*:887-889 (1981).	
JKL	110 !	Huang et al., "Active site general catalysts are not necessary for some proton transfer reactions of thymidylate synthase" *Biochem. 36*:1869-1873 (1997).	
JKL	111 !	Hudziak et al., "Amplified expression of the HER2/ERBB2 oncogene induces resistance to tumor necrosis factor I in NIH 3T3 cells" *PNAS USA 85*:5102-5106 (1988).	
JKL	112 !	Hudziak et al., "Selection for transformation and *met* protooncogene amplification in NIH 3T3 fibroblasts using tumor necrosis factor I" *Cell Growth & Differentiation 1*:129-134 (1990).	
JKL	113 !	Husak, R. et al. "Pseudotumour of the tongue caused by herpes simplexx virus type 2 in an HIV-1 infected immunosuppressed patient" *British J. Dermatol.* 139:118-121 (1998)	
JKL	114 !	Imai et al., "Studies on phosphorylation. IV. Selective phosphorylation of the primary hydroxyl group in nucleosides" *J. Org. Chem. 34*(6):1547-1550 (1969).	
JKL	115 !	Jackman et al., "Quinazoline-based thymidylate synthase inhibitors: Relationship between structural modifications and polyglutamation" *Anti-Cancer Drug Design 10*:573-589 (1995).	
JKL	116 !	Johnston et al., "Production and characterization of monoclonal antibodies that localize human thymidylate synthase in the cytoplasm of human cells and tissue" *Can. Res. 51*:6668-6676 (1991).	
JKL	117 !	Johnston, "The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer" *J. Clin. Oncol. 12*(12):2640-2647 (1994).	
JKL	118 !	Kamb et al., "Cyclin-dependent kinase inhibitors and human cancer" *Curr. Top. Microbiol. Immunol. 227*:139-148 (1998).	
JKL	119 !	Kashani-Sabet et al., "Detection of drug resistance in human tumors by *in vitro* enzymatic amplification" *Can. Res. 48*:5775-5778 (1988).	

! Month of publication data is unavailable for this citation.

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

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	120	Katki, A.G. et al. "Prodrugs activated by thymidylate synthase: Treatment of tumors with deoxyuridine analogs" *Proc. Amer. Assoc. Cancer Res.* 39, Abstract No. 1275 (March 1998)	
	121 !	Klecker et al., "Toxicity, metabolism, DNA incorporation with lack of repair, and lactate production for 1-(2'-fluoro-2'-deoxy-J-D-arabinofuranosyl)-5-iodouracil in U-937 and MOLT-4 cells" *Mol. Pharmacol. 46*:1204-1209 (1994).	
	122 !	Knighton et al., "Structure and kinetic channelling in bifunctional dihydrofolate reductase-thymidylate synthase" *Nature Struct. Biol. 1*(3):186-194 (1994).	
	123 !	Kobayashi et al., "Effect of hammerhead ribozyme against human thymidylate synthase on the cytotoxicity of thymidylate synthase inhibitors" *Jpn. J. Can. Res. 86*:1014-1018 (1995).	
	124 !	Kodama, E. et al. "Evaluation of antiherpetic compounds using a gastric cancer cell line: Pronounced activity of BVDU against herpes simplex virus replication" *Microbiol. Immunol.* 40(5):359-363 (1996)	
	125 !	Kumar et al., "Synthesis and biological evaluation of some cyclic phosphoramidate nucleoside derivatives" *J. Med. Chem. 33*(9):2368-2735 (1990).	
	126 !	Kundu, "Synthesis and biological activities of [E]-5-(2-acylvinyl) uracils" *Eur. J. Med. Chem. 28*:473-479 (1993).	
	127 !	Kuroboshi et al., "A facile synthesis of difluoromethylene compounds by oxidative fluorodesulfurization of dithioacetals using tetrabutylammonium dihydrogentrifluoride and *N*-halo compounds" *SYNLETT*:909-910 (1991).	
	128 !	Kuroboshi et al., "A facile synthesis of l,l-difluoroalkyl ethers and carbonyl fluoride acetals by oxidative desulfurization-fluorination" *SYNLETT*:251-252 (1994).	
	129 !	Lam, "Application of combinatorial library methods in cancer research and drug discovery" *Anticancer Drug Design 12*:145-167 (1997).	
	130 !	Larsson, P.A., et al. "Thymidylate synthase in advanced gastrointestinal and breast cancers" *Acta Oncologica* 35(4):469-472 (1996)	
	131 !	Lasic, "Doxorubicin in sterically stabilized liposomes" *Nature 380*:561-562 (1996).	
	132 !	Lewis et al., "A serum-resistant cytofection for cellular delivery of antisense oligodeoxynucleotides and plasmid DNA" *PNAS USA. 93*:3176-3181 (1996).	
	133 !	Li et al., "Lack of functional retinoblastoma protein mediates increased resistance to antimetabolites in human sarcoma cell lines" *PNAS USA 92*:10436-10440 (1995).	
	134 !	Lin et al., "Rhenium-188 hydroxyethylidene diphosphonate: A new generator-produced radiotherapeutic drug of potential value for the treatment of bone metastases" *Eur. J. Nucl. Med. 24*(6):590-595 (1997).	
	135 !	Livak et al., "Detection of single base differences using biotinylated nucleotides with very long linker arms" *Nucl. Acids Res. 20*(18):4831-4837 (1992).	
	136 !	Livingstone, L.R. et al., "Altered cell cycle arrest and gene amplification potential accompany loss of wild-type p53" *Cell 70*:923-935 (1992).	
	137 !	Lönn et al., "Higher frequency of gene amplification in breast cancer patients who received adjuvant chemotherapy" *Cancer 77*(1):107-112 (1996).	
	138 !	Lovejoy et al., "Animal models and the molecular pathology of cancer" *J. Pathol. 181*:130-135 (1997).	
	139 !	Masters et al., "The nucleotide sequence of the cDNA coding for the human dihydrofolic acid reductase" *Gene 21*:59-63 (1983).	
	140 !	McGuigan, "Aryl phosphate derivatives of AZT retain activity HIV1 in cell lines which are resistant to the action of AZT" *Antiviral Res. 17*:311-321 (1992)	
	141 !	McGuigan, "Intracellular delivery of bioactive AZT nucleotides by aryl phosphate derivatives of AZT" *J. Med. Chem. 36*:1048-1052 (1993)	
	142 !	McGuigan et al., "Certain phosphoramidate derivatives of dideoxy uridine (ddU) are active against HIV and successfully by-pass thymidine kinase" *FEBS Let 351*:11-14 (1994)	
	143 !	McGuigan, "Aryl phosphoramidate derivatives of d4T have improved anti-HIV efficacy in tissue culture and may act by the generation of a novel intracellular metabolite" *J. Med. Chem. 39*:1748-1753 (1996).	
	144 !	McGuigan et al., "Synthesis and evaluation of some masked phosphate esters of the anti-herpetic drug 882C (netivudine) as potential antiviral agents" *Antiviral Chem. Chemother. 9*:187-197 (1998).	
	145 !	McIntee, "Probing the mechanism of action and decomposition of amino acid phosphomonoester amidates of antiviral nucleoside prodrugs" *J. Med. Chem. 40*:3323-3331 (1997).	
	146 !	McKay et al., "Broad spectrum aminoglycoside phosphotransferase type III from *Enterococcus*: Overexpression, purification, and substrate specificity" *Biochem 33*:6936-6944 (1994).	
	147 !	Meden et al., "Elevated serum levels of a c-erbB-2 oncogene product in ovarian cancer patients and in pregnancy" *J. Can. Res. Clin. Oncol. 120*:378-381 (1994).	
	148 !	Meier et al., "ADA-bypass by lipophilic *cyclo*sal-ddAMP pro-nucleotides a second example of the efficiency of the *cyclo*sal-concept" *Bioorg. Med. Chem. Lett. 7*(12):1577-1582 (1997).	
	149 !	Meier et al., "Cyclic saligenyl phosphotriesters of 2',3'-dideoxy-2',3'-didehydrothymidine (d4T)- a new pro-nucleotide approach" *Bioorg. Med. Chem. Lett. 7*(2):99 (1997).	
	150 !	Meier et al., "*Cyclo*Sal-pro-nucleotides: The design and biological evaluation of a new class of lipophilic nucleotide prodrugs" *Int'l. Antiviral News 5*(10):183-185 (1997).	
	151 !	Melton et al., "Antibody-enzyme conjugates for cancer therapy" *J. Natl. Can. Inst. 88*(3/4):153-165 (1996).	
	152 !	Montfort et al., "Thymidylate synthase: Structure, inhibition, and strained conformations during catalysis" *Pharmacol. Ther. 76*(1-3):29-43 (1997).	
	153 !	Montgomery et al., "Phosphonate analogue of 2!-deoxy-5-fluorouridylic acid" *J. Med. Chem. 22*(1):109-111 (1979).	
	154 !	Morgan et al., "Tumor efficacy and bone marrow-sparing properties of TER286, a cytotoxin activated by glutathione *S*-transferase" *Can. Res. 58*:2568-2575 (1998).	
	155 !	Murakami et al., "Accumulation of genetic alterations and their significance in each primary human cancer and cell line" *Mutat. Res. 400*(1-2):421-437 (1998).	

! Month of publication data is unavailable for this citation.

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher city and/or country where published	T[2]
	156	Nakano et al., "Critical role of phenylalanine 34 of human dihydrofolate reductase in substrate and inhibitor binding and in catalysis" *Biochem. 33*:9945-9952 (1994).	
	157	Nooter et al., "Molecular mechanisms of multidrug resistance in cancer chemotherapy" *Pathol. Res. Pract. 192*:768-780 (1996).	
	158	Osaki et al., "5-fluorouracil (5-FU) induced apoptosis in gastric cancer cell lines: Role of the p53 gene" *Apoptosis 2*:221-226 (1997).	
	159	Oshiro, Y. et al. "Genotoxic properties of *(E)*-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)" *Fund. Appl. Toxicol.* 18:491-498 (1992)	
	160	Pardo et al. "The incorporation of deoxyuridine monophosphate in DNA increases the sister-chromatid exchange yield" *Exp Cell Res.* 168:507-517 (1987)	
	161	Park, N.H. et al. "Chemotherapy efficacy of E-5-(2-bromovinyl)-2'-deoxyuridine for orofacial infection with herpes simplex virus type 1 in mice" *J. Infectious Diseases* 145(6):909-913 (1982)	
	162	Perry et al. "Plastic adaptation toward mutations in proteins: Structural comparison of thymidylate synthases" *Proteins 8*:315-333 (1990).	
	163	Pestalozzi et al., "Prognostic importance of thymidylate synthase expression in early breast cancer" *J. Clin. Oncol. 15*(5):1923-1931 (1997).	
	164	Peters et al., "Thymidylate synthase and drug resistance" *Eur. J. Can. 31A*(7/8):1299-1305 (1995).	
	165	Phelps et al., "Synthesis and biological activity of 5-fluoro-2'-deoxyuridine 5'-phosphorodiamidates" *J. Med. Chem. 23*:1229-1232 (1980).	
	166	Pupa et al., "The extracellular domain of the c-*erb*B-2 oncoprotein is released from tumor cells by proteolytic cleavage" *Oncogene 8*:2917-2923 (1993).	
	167	Roberts, "An isotopic assay for thymidylate synthetase" *Biochem. 5*(11):3546-3548 (1966).	
	168	Robins et al., "Nucleic acid related compounds. 31. Smooth and efficient palladium-copper catalyzed coupling of terminal alkynes with 5-iodouracil nucleosides" *Tetrahedron Lett. 22*:421-424 (1981).	
	169	Robins et al., "Nucleic acid related compounds. 38. Smooth and high-yield iodination and chlorination at C-5 of uracil bases and *p*-toluyl-protected nucleosides" *Can. J. Chem. 60*:554-557 (1982).	
	170	Robins et al., "Nucleic acid compounds. 39. Efficient conversion of 5-iodo to 5-alkynyl and derived 5-substituted uracil bases and nucleosides" *J. Org. Chem. 48*:1854-1862 (1983).	
	171	Rogulski, K.R. et al. "Glioma cells transduced with an *Escherichia coli* CD/HSV-1 TK fusion gene exhibit enhanced metabolic suicide and radiosensitivity" *Hum. Gene Ther.* 8:73-85 (1997)	
	172	Roninson et al., "Amplification of specific DNA sequences correlates with multi-drug resistance in chinese hamster cells" *Nature 309*:626-628 (1984).	
	173	Ruth et al., "C-5 sustituted pyrimidine nucleosides. 1. Synthesis of C-5 allyl, propyl, and propenyl uracil and cytosine nucleosides via organopalladium intermediates" *J. Org. Chem. 43*(14):2870-2876 (1978).	
	174	Santi, "Perspectives on the design and biochemical pharmacology of inhibitors of thymidylate synthetase" *J. Med. Chem. 28*(2):103-111 (1980).	
	175	Sastry et al., "Membrane-permeable dideoxyuridine 5'-monophosphate analogue inhibits human immunodeficiency virus infection" *Mol. Pharmacol. 41*:441-445 (1992).	
	176	Sauter et al., "Heterogeneity of *erb*B-2 gene amplification in bladder cancer" *Can. Res. 53*:2199-2203 (1993).	
	177	Schiffer et al., "Crystal structure of human thymidylate synthase: A structural mechanism for guiding substrates into the active site" *Biochem. 34*:16279-16287 (1995).	
	178	Schimke, "Gene amplification in cultured cells" *J. Biol.Chem. 263*(13):5989-5992 (1988).	
	179	Segovia, "*Leishmania* gene amplification: A mechanism of drug resistance" *Annals Tropical Med. Parasitol. 88*(2):123-130 (1994).	
	180	Shepard et al., "Resistance of tumor cells to tumor necrosis factor" *J. Clin. Immunol. 8*(5):333-341 (1988).	
	181	Simon, "Cell biological mechanisms of multidrug resistance in tumors" *PNAS USA 91*:3497-3504 (1994).	
	182	Singh et al., "Studies on the preparation and isomeric composition of 186Re- and 188Re-pentavalent rhenium dimercaptosuccinic acid complex" *Nucl. Med. Commun. 14*:197-203 (1993).	
	183	Slamon et al., "Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/*neu* oncogene" *Science 235*:177-182 (1987).	
	184	Slamon et al., "Studies of the HER-2/*neu* proto-oncogene in human breast and ovarian cancer" *Science 244*:707-712 (1989).	
	185	Smith et al., "Regulation and mechanisms of gene amplification" *Phil. Trans. Royal Soc. Lond. B 347*:49-56 (1995).	
	186	Snydman et al., "Analysis of trends in antimicrobial resistance patterns among clinical isolates of *Bacteroides fragilis* group species from 1990 to 1994" *Clin. Infectious Diseases 23*(Suppl. 1):S54-S65 (1996).	
	187	Staschke, K.A. et al. "The in vitro anti-hepatitis B virus activity of FIAU [1-(2'-deoxy-2'-fluro-1-β-D-arabinofuranosyl-5-iodo)uracil] is selective, reversible, and determined, at least in part, by the host cell" Antiviral Res. 23:45-61 (1994)	
	188	Stout et al., "Structure-based design of inhibitors specific for bacterial thymidylate synthase" *Biochem. 38*:1607-1617 (1999).	
	189	Stühlinger et al., "Clinical therapy and HER-2 oncogene amplification in breast cancer: Chemo-vs radiotherapy" *J. Steroid Biochem. Molec. Biol. 49*(1):39-42 (1994).	
	190	Sugarman et al., "Recombinant human tumor necrosis factor-I: Effects on proliferation of normal and transformed cells in vitro" *Science 230*(4728):943-945 (1985).	
	191	Sukumar et al., "Specific patterns of oncogene activation in transplacentally induced tumors" *PNAS USA 87*:718-722 (1990).	

! Month of publication data is unavailable for this citation.

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher city and/or country where published	T[2]
	192 !	Takeishi et al., "Nucleotide sequence of a functional cDNA for human thymidylate synthase" *Nucl. Acid Res. 13*(6):2035-2043 (1985).	
	193 !	Tannock, "Treatment of cancer with radiation and drugs" *J. Clin. Oncol. 14*(12):3156-3174 (1996).	
	194 !	Tennant et al., "Antiviral activity and toxicity of fialuridine in the woodchuck model of hepatitis B virus infection" *Hepatol. 28*(1):179-191 (1998).	
	195 !	Tolstikov et al., "Synthesis and DNA duplex stabilities of oligonucleotides containing C-5-(3-methoxypropynyl)-2'-deoxyuridine residues" *Nucleosides Nucleotides 16*(3):215-225 (1997).	
	196 !	Troutner, "Chemical and physical properties of radionuclides" *Nucl. Med. Biol. 14*(3):171-176 (1987).	
	197 !	Ubeda et al., "The large subunit of the DNA replication complex C (DSEB/RF-C140) cleaved and inactivated by caspace-3 (CPP32/YAMA) during fas-induced apoptosis" *J. Biol. Chem. 272*(31):19562-19568 (1997).	
	198 !	Valette et al., "Decomposition pathways and *in vitro* HIV inhibitory effects of isoddA pronucleotides: Toward a rational approach for intracellular delivery of nucleoside 5'-monophosphates" *J. Med. Chem. 39*:1981 (1996).	
	199 !	Van de Vijver et al., "Amplification of the *neu* (c-*erbB*-2) oncogene in human mammary tumors is relatively frequent and is often accompanied by amplification of the linked c-*erbA* oncogene" *Mol. Cell. Biol. 7*(5):2019-2023 (1987).	
	200 !	Volm et al., "Relationship of inherent resistance to doxorubicin, proliferative activity and expression of P-glycoprotein 170, and glutathione S-transferase-X in human lung tumors" *Cancer 70*(4):764-769 (1992).	
	201 !	Wahba et al., "Direct spectrophotometric evidence for the oxidation of tetrahydrofolate during the enzymatic synthesis of thymidylate" *J. Biol. Chem. 236*(3):C11-C12 (1961).	
	202 !	Wang et al., "Identification and characterization of Ich-3, a member of the interleukin-1J converting enzyme (ICE)/Ced-3 family and an upstream regulator of ICE" *J. Biol. Chem. 271*(34):20580-20587 (1996).	
	203 !	Wataya et al., "Trans-5-(3,3,3-trifluoro-1-propenyl)-2'-deoxyuridylate: A mechanism-based inhibitor of thymidylate synthetase" *J. Med. Chem. 22*(4):339-340 (1979).	
	204 !	Wettergren et al., "Drug-specific rearrangements of chromosome 12 in hydroxyurea-resistant mouse SEWA cells: Support for chromosomal breakage model of gene amplification" *Somatic Cell Mol. Genet. 20*(4):267-285 (1994).	
	205 !	Yen et al., "Characterization of a hydroxyurea-resistant human KB cell line with supersensitivity to 6-thioguanine" *Can. Res. 54*:3686-3691 (1994).	
	206 !	Yin et al., "Wild-type p53 restores cell cycle control and inhibits gene amplification in cells with mutant p53 alleles" *Cell 70*:937-948 (1992).	
	207 !	Zhou et al., "Target protease specificity of the viral serpin CrmA" *J. of Biol. Chem. 272*(12):7797-7800 (1997).	

! Month of publication data is unavailable for this citation.

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Application Number	**09/782,721**
Filing Date	**February 12, 2001**
First Named Inventor	**H. Michael SHEPARD**
Art Unit	1623 ~~1653~~
Examiner Name	**L. Crane**
Attorney Docket Number	**NB 2004.02**

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number – Number – Kind Code[2] (if known)	Publication Date MM-DD-YY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
LCE	B 1	US-4,668,777	05-26-87	Caruthers et al.	
LCE	B 2	US-4,963,263	10-16-90	Kauver	
LCE	B 3	US-4,963,533	10-16-90	De Clercq et al.	
LCE	B 4	US-5,116,822	05-26-92	De Clercq et al.	
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LCE	B 6	US-5,137,724	08-11-92	Balzarini et al.	
LCE	B 7	US-5,217,869	06-08-93	Kauver	
LCE	B 8	US-5,300,425	04-05-94	Kauver	
LCE	B 9	US-5,338,659	08-16-94	Kauver, et al.	
LCE	B 10	US-5,430,148	07-04-95	Webber, et al.	
LCE	B 11	US-5,433,955	07-18-95	Bredehorst et al.	
LCE	B 12	US-5,516,631	05-14-96	Frisch	
LCE	B 13	US-5,527,900	06-18-96	Balzarini et al.	
LCE	B 14	US-5,596,018	01-21-97	Baba et al.	
LCE	B 15	US-5,733,896	03-31-98	Holý et al.	
LCE	B 16	US-5,968,910	10-19-99	Balzarini	
LCE	B 17	US-6,057,305	05-02-00	Holý et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document – Country Code[3] – Number[4] – Kind Code[5] (if known)	Publication Date MM-DD-YY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
LCE	B 18	DE 32 29 169 A1	02-09-84	De Clercq et al.		
LCE	B 19	EP 0 311 107 A2	04-12-89	Stichting REGA VZW		
LCE	B 20	EP 0 311 108A2	04-12-89	Stichting REGA VZW		
LCE	B 21	EP 0 316 592	05-24-89	Stichting REGA VZW		
LCE	B 22	WO 90/03978	04-19-90	Stichting REGA VZW		
LCE	B 23	WO 92/19767	11-12-92	Terrapin Technologies, Inc.		

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First Named Inventor	H. Michael SHEPARD
Art Unit	1623 ~~1653~~
Examiner Name	L. Crane
Attorney Docket Number	NB 2004.02

FOREIGN PATENT DOCUMENTS

	B 24	WO 95/09865	04-13-95	Terrapin Technologies, Inc.		
	B 25	WO 96/40739	12-19-96	Terrapin Technologies, Inc.		
	B 26	WO 97/25342	07-17-97	Terrapin Technologies, Inc.		
	B 27	WO 97/49717	12-31-97	Balzarini et al.		
	B 28	WO 98/49177	11-05-98	University College Cardiff Consultants Limited		
	B 29	WO 00/18755	04-06-00	University College Cardiff Consultants Limited and Rega Foundation		
	B 30	WO 01/83501	11-08-01	University College Cardiff Consultants Limited and Rega Foundation		
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OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

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	C 1 !	BAJETTA, E. et al. "A pilot safety study of capecitabine, a new oral fluoropyrimidine, in patients with advanced neoplastic disease" *Tumor* (1996) **82**:450-452	
	C 2 !	CODERRE, J.A. et al. "Mechanism of action of 2',5-difluoro-1-arabinosyluracil" *J. Med. Chem.* (1983) **26(8)**:1149-1152	
	C 3	MEAD, J.A.R. et al. "Pharmacologic aspects of homofolate derivatives in relation to amethopterin-resistant murine leukemia" *Cancer Res.* (November 1966) **26(1)**:2374-2379 (November, 1966).	
	C 4	NICHOL, C.A. and M.T. HAKALA "Comparative growth-inhibitory activity of homofolic acid against cell lines sensitive and resistant to amethopterin" *Biochem. Pharmacol.* (October 1966) **15(10)**:1621-1623 (October, 1966).	
	C 5 !	RODE, W. "Specificity of thymidylate synthase inactivation by 4,5-bisubstituted dUMP analogues" M. Nencki Inst. Exp. Biol., *Acta Biochimica Polonica* (1993) **40(3)**:363-368	
	C 6 !	SATYAM, A. et al. "Design, synthesis, and evaluation of latent alkylating agents activated by glutathione s-transferase" *J. Med. Chem.* (1996) **39**:1736-1747	
	C 7	WATAYA, Y. et al. "Interaction of thymidylate synthetase with 5-nitro-2'-deoxyuridylate" *J. Biol. Chem.* (June 1980) **255(12)**:5538-5544	

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! Month of publication could not be determined from the copy supplied.

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